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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
GRASER, JENNIFER E	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 07/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/720,192	LAQUEYRERIE ET AL.	
	Examiner	Art Unit	
	Jennifer E. Graser	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 June 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-21 and 23-30* is/are pending in the application.

4a) Of the above claim(s) *20,21,23,24 and 27-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19,25 and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 November 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, claims 19, 25 and 26, in the reply filed on 6/28/04 is acknowledged. The traversal is on the ground(s) that the Examiner did not cite that it would be a serious burden to examine all of the claims together and that the claims must be either independent or distinct to be restricted. It is further argued that not enough Examples were provided to support the Examiner's position. This is not found persuasive because the Examiner followed the MPEP Restriction Guidelines to the letter, even using the custom form action program to write the Restriction Requirement. The explanation that Applicants argue is inadequate is the one generated through the MPEP program and is standard USPTO Restriction Practice. The "process of making and product made" explanation is taken directly from process (MPEP 806.05(f)). It is suggested that Applicant's Representative review this section of the MPEP. Further, the Restriction Requirement specifically states that because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, as shown by their different classification, and because the literature search for Groups I -III would not be coextensive, restriction for examination purposes as indicated is proper. A literature search which is not coextensive would inherently place an undue burden on the Examiner. Additionally, paragraph 2 of the Restriction Requirement states: The inventions are distinct, each from the other because of the following reasons: The products of Groups I and II/III are biologically, chemically and structurally different and

therefore are patentably distinct and independent inventions. It is not necessary for the Examiner to have to explain how an antibody, a protein and a nucleic acid are structurally, chemically and biologically different as this is common knowledge and readily apparent to those of the most ordinary skill in the art. Lastly, this same Restriction Requirement was provided in the four parent cases which are now all Patented Cases. The elected invention was examined and allowed in parent application 09/985,372.

The requirement is still deemed proper and is therefore made **FINAL**.

Specification

2. The current status of all nonprovisional parent applications referenced should be updated in the first paragraph of the specification. Specifically, the patent number of 09/985,372 should be included.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 19, 25 and 26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 19 is vague and indefinite because it is unclear what is encompassed by "at least a portion' of the amino acid sequence of SEQ ID NO:2 or 3". 'At least a portion' reads on as few as one or two amino acids. The claim is also vague and indefinite because of the phrase "having secondary differences or limited variations". It

is unclear what structures would be encompassed by this terminology. What is meant by "secondary differences" and how are the variations 'limited'? Clarification is requested.

Claims 19, 25 and 26 are vague and indefinite because it is unclear what type of polypeptide may be linked to the polypeptide of SEQ ID NO:2 or 3. Does this polypeptide have to be an antigen or an adjuvant? Is the polypeptide a carrier or a hapten. Clarification is requested.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 19, 25 and 26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for "a hybrid protein comprising a polypeptide having the amino acid sequence of SEQ ID NO:2 or SEQ ID NO:3 linked to an antigenic polypeptide which is able to induce an immune response in an animal" and pharmaceutical compositions and compositions comprising said hybrid protein , does not reasonably provide enablement for "a hybrid protein comprising at least a portion of the amino acid sequence of SEQ ID NO:2 or SEQ ID NO:3"; or a protein having secondary differences or limited variations in the amino acid sequences of SEQ ID NO: 2 or SEQ ID NO:3 and a polypeptide which is able to induce an immune response in an animal" and pharmaceutical compositions and compositions comprising said hybrid protein. The specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to hybrid proteins and pharmaceutical compositions comprising said hybrid proteins which comprise "at least a portion" of the protein of SEQ ID Nos.: 2 or 3; and proteins having secondary differences or limited variations in the amino acid sequence of SEQ ID NO:2 or 3. However, the specification provides no guidance as to what these changes or differences may be. The breadth of the instant claims contain amino acid sequences other than what is specified in the sequence disclosure. The specification states that substitutions, additions, or deletions may be made to the defined sequences; however, the specification provides no guidance as to what amino acids may be changed without causing a detrimental effect to the protein to be produced. Further, it is unpredictable as to which amino acids could be removed and which could be added. While it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where amino acid substitutions can be made with a reasonable expectation of success are limited. Other positions are critical to the protein's structure/function relationship, e.g., such as various positions or regions directly involved in binding, catalysis in providing the correct three-dimensional spatial orientation of binding and catalytic sites. These regions can tolerate only very little or no substitutions. Selective could eliminate the ability of an antibody to recognize this altered antigen. If the range of decreased binding ability after single point mutation of a protein antigen varies, one could expect point mutations in the protein antigen to cause varying degrees of loss of protection, depending on the relative

importance to the binding interaction of the altered residue. Alternatively, the combined effects of multiple changes in an antigenic determinant could again result in loss of protection. A protein having multiple antigenic sites, multiple point mutations, or accumulated point mutations at key residues could create a new antigen that is precipitously or progressively unrecognizable by any of the antibodies in the polyclonal pool. Thus, proteins of different levels of homology may not induce antibody which is recognized by the "native" protein on the *Mycobacteria*, and be ineffective in treating or inducing an immune response against disease caused by *Mycobacteria*.

The specification states that the vaccines may be used to immunize individuals against tuberculosis (p. 13, lines 6-10). The specification states that guinea pigs were immunized with live Mycobacteria or heat-killed bacteria; however, the specification does not teach any immunization protocols which utilize the protein which comprises "at least a portion" of the protein of SEQ ID Nos.: 2 or 3. No protocols are provided which detail immunization procedures. Protein vaccines/compositions are highly unpredictable and although some vaccines may produce antibodies these antibodies may confer no protection against the disease they are intended to prevent. It is unclear from the teachings provided in the specification if the entire protein of SEQ ID No: 2 or 3 would have success as a vaccine/pharmaceutical composition and it is even more uncertain which portions of the protein could be used as a vaccine/pharmaceutical composition. As no immunization protocols are provided in the instant specification and no working examples which would suggest that the protein would have a reasonable expectation of success in a pharmaceutical composition, it would take one

of skill in the art undue experimentation to practice the claimed invention. Further, it is unclear that the protein or a portion of it would have use as a drug. It is unclear that the protein would provide an immunotherapeutic effect. Given the lack of guidance contained in the specification and the unpredictability for determining acceptable amino acid substitutions, one of skill in the art could not make or use the broadly claimed invention without undue experimentation.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 19, 25 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wieles et al (Infect. Immun. Jan. 1994. 62(1): 252-258) in view of Marchal et al (WO 92/21758) Note: US 6,060,259 was used for English translation of the WO patent.

Wieles et al disclose a protein antigen from *M.leprae* which is related to the secreted *M.tuberculosis* protein MPT32(abstract). The protein disclosed by Wieles et al has "at least a portion of the sequence SEQ ID NO. 2 and 3". Figure 17 and page 8, lines 20-23, of Applicant's specification teach the homology of Wieles' protein to the proteins disclosed in SEQ ID Nos: 2 and 3. Sequence analysis revealed that the protein of Wieles has an overall similarity of 60% and a best local similarity of 68.6% to

Applicants' SEQ ID NO: 2 and 3. Immunological assays comprising the protein and a detection agent were performed (p. 254 and p. 256).

However, Wieles et al do not teach a the use of their protein antigens in a hybrid protein.

Marchal et al disclose proteins from *Mycobacterium bovis* which have a molecular weight of approximately 44.5 to 47.5 kD. Said proteins have molecular weights of about 45 kD or about 47 kD and isoelectric pH values of about 3.7 (45 and 47 kD proteins) and 3.9 (47 kD proteins). Proteins or hybrid proteins comprising a part of their sequences may be used as vaccines or medicaments, or for the detection and monitoring of tuberculosis, in particular in humans and in cattle. The reference teaches that hybrid proteins comprising the whole or part of the 45-47kDa *Mycobacterium* proteins and a sequence corresponding to an antigenic determinant. It is taught that the antigenic determinant can be a fragment of a protein or glycoprotein antigen, in order to obtain immunogenic compositions able to induce the synthesis of antibodies directed against these multiple antigenic determinants. It is taught that the antigenic determinants or fragments may be, for example, diphtheria toxin or fragments thereof, tetanus toxin, the surface antigen of hepatitis B virus, poliomyelitis virus VP1 antigen, etc. These hybrid proteins allow for a dual immune response which includes immunization to antigenic determinants not present on the *Mycobacterium* proteins. See column 4, lines 13-35.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made that all or part of the *Mycobacterium* proteins disclosed by

Wieles et al could be used to form a hybrid protein comprising a antigenic polypeptide which can induce antibodies in a host because Marchal et al teach similar and related *Mycobacterial* proteins to those disclosed by Wieles et al and teaches that these proteins linked to antigenic protein or fragment of a protein or glycoprotein antigen, can be used to obtain immunogenic compositions able to induce the synthesis of antibodies directed against these multiple antigenic determinants. Marchal teaches that the antigenic determinants or fragments may be, for example, diphtheria toxin or fragments thereof, tetanus toxin, the surface antigen of hepatitis B virus, poliomyelitis virus VP1 antigen, etc. One of ordinary skill in the art would have been motivated to make hybrid proteins using the proteins taught by Wieles and an antigenic polypeptide such as those taught by Marchal et al. because the proteins of Marchal are homologous to those taught by Wieles and one of ordinary skill in the art would have a reasonable expectation of achieving a strong dual immune response in a host through the administration of said hybrid proteins.

Double Patenting

9. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

10. Claims 19, 25 and 26 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 6,676,945. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims recite the use of "at least a portion" of SEQ ID Nos: 2 or 3, whereas the patented claims recite the use of one of the full-length proteins of SEQ ID NO:2 or 3 in the hybrids. The scope of the instant claims and the patented claims would be obvious, each over the other, as "at least a portion" includes the full-length sequences.

NOTE: The elected claims were presented in parent case, now US Patent No. 6,676,945. These claims were amended during the prosecution of the parent case in order to overcome the 112, 1st and 2nd paragraph and prior art rejections which is why they are now different from the pending claims. It is brought to Applicants intention that if the claims are amended in a similar manner the following ***Statutory*** Double Patenting Rejection will be made:

Claims 19, 25 and 26 are rejected under the judicially created doctrine of double patenting over claims 1-12 of U. S. Patent No. 6,676,945 since **the claims, if allowed, would improperly extend the "right to exclude" already granted in the patent.**

The subject matter claimed in the instant application is fully disclosed in the patent and is covered by the patent since the patent and the application are claiming common subject matter, as follows: hybrid proteins comprising SEQ ID Nos: 2 or 3 and an antigenic polypeptide.

Furthermore, there is no apparent reason why applicant was prevented from presenting claims corresponding to those of the instant application during prosecution of the application which matured into a patent. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

11. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15,1989). The Group 1645 Fax number is (703) 308-4242 which is able to receive transmissions 24 hours/day, 7 days/week.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer E. Graser whose telephone number is (703) 308-1742. The examiner can normally be reached on Monday-Friday from 7:00 AM-4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909.

JGraser 7/22/04

Jennifer Graser
Primary Examiner
Art Unit 1645